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Relation of Perfusion Defects Observed With Myocardial Contrast Echocardiography to the Severity of Coronary Stenosis: Correlation With Thallium-201 Single-Photon Emission Tomography

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It has been previously shown that myocardial contrast echocardiography is a valuable technique for delineating regions of myocardial underperfusion secondary to coronary occlusion and to critical coronary stenoses in the presence of hyperemic stimulation. The aim of this study was to determine whether myocardial contrast echocardiography performed with a stable solution of sonicated albumin could detect regions of myocardial underperfusion resulting from various degrees of coronary stenosis. The perfusion defect produced in 16 open chest dogs was compared with the anatomic area at risk measured by the postmortem dual-perfusion technique and with thallium-201 single-photon emission tomography (SPECT).

During a transient (20-s) coronary occlusion, a perfusion defect was observed with contrast echocardiography in 14 of the 15 dogs in which the occlusion was produced. The perfusion defect correlated significantly with the anatomic area at risk ($r = 0.74$; $p < 0.002$).

During dipyridamole-induced hyperemia, 12 of the 16 dogs with a partial coronary stenosis had a visible area of hypoperfusion by contrast echocardiography. The four dogs without a perfusion defect had a stenosis that resulted in a mild (0% to 50%) reduction in dipyridamole-induced hyperemia. The size of the perfusion defect during stenosis correlated significantly with the anatomic area at risk ($r = 0.61$; $p = 0.02$). Thallium-201 SPECT demonstrated a perfusion defect in all 14 dogs analyzed during dipyridamole-induced hyperemia; the size of the perfusion defect correlated with the anatomic area at risk ($r = 0.58$; $p < 0.03$) and with the perfusion defect by contrast echocardiography ($r = 0.58$; $p < 0.03$).

Thus, myocardial contrast echocardiography can be used to visualize and quantitate the amount of jeopardized myocardium during moderate to severe degrees of coronary stenosis. The results obtained show a correlation with the anatomic area at risk similar to that obtained with thallium-201 SPECT.

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Myocardial contrast echocardiography has undergone extensive validation in the animal laboratory as a method for the in vivo detection and quantification of underperfused myocardium (1–7). We have previously found (8) that myocardial contrast echocardiography performed with sonicated diatrizoate meglumine can delineate areas of underperfused myocardium after coronary occlusion and after the administration of dipyridamole in the presence of a critical coronary artery stenosis. The current investigation was designed to determine whether myocardial contrast echocardiography during a hyperemic stimulus could be used to differentiate normal myocardial regions from regions supplied by a coronary artery with a noncritical stenosis. Furthermore, the size of the myocardial perfusion defects observed by myocardial contrast echocardiography was compared with that of the perfusion defects observed during simultaneous thallium-201 single-photon emission computed tomography (SPECT) and with anatomic areas at risk determined by the postmortem dual-perfusion technique.

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Methods

Animal preparation. Sixteen mongrel dogs weighing 27 ± 5 kg (mean ± SD) were anesthetized with 30 mg/kg body weight of sodium pentobarbital and 0.5 mg/kg of xylazine intravenously, intubated and artificially ventilated with a Harvard respirator. The heart was exposed through a left thoracotomy and suspended in a pericardial cradle filled with warm water. A cannula was placed in the left atrium for the administration of radioactive microspheres. Catheters were placed in the right carotid artery for continuous blood

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pressure monitoring and microsphere reference blood sampling, in the jugular vein for administration of thallium-201 and in a peripheral vein for administration of fluids and drugs. A modified pigtail catheter was positioned in the proximal aortic root just above the aortic valve for administration of sonicated albumin.

The proximal left anterior descending and left circumflex coronary arteries were dissected free from surrounding tissues and silk ties were loosely placed around them. Distal to the position of the ties, an epicardial Doppler flow velocity probe was placed snugly around each vessel. One of the ties was used to occlude the selected artery (the left anterior descending artery in eight dogs and the left circumflex artery in the remaining eight dogs) and the other tie was attached to a vascular Schwartz clamp and used to create the various stenoses (8). Continuous recordings of arterial pressure, an electrocardiogram (ECG) and Doppler flow velocity signals were performed on an eight-channel Gould-Brush strip chart recorder.

This study conformed to the "Position of the American Heart Association on Research Animal Use" adopted November 11, 1984.

Establishment of a coronary stenosis. Before the creation of a coronary stenosis, the maximal hyperemic response was assessed with the Doppler flow velocity probe by transiently occluding (20 s) the left circumflex or left anterior descending coronary artery. One stenosis was created in each dog in the selected artery by stepwise tightening of the vascular clamp followed each time by a 20-s occlusion to determine the effect of the stenosis on reactive hyperemia. Guided by the degree of reduction in maximal hyperemia, a different level of ligature stenosis was created in each dog in an attempt to obtain a range of stenoses in the 16 dogs. The severity of the stenosis was ultimately determined by the reduction in coronary reserve ratio as determined by microspheres.

Echocardiographic imaging (Table 1). Echocardiographic studies were performed by using a commercially available phased array scanner equipped with a 3.5-MHz transducer (Hewlett-Packard, model 77020 AC). Images of the left ventricle were obtained in a short-axis cross-sectional view at the mid-papillary muscle level. The transducer position was fixed at the beginning of the experiment by using a clamp affixed to a metal stand and was not changed for the remainder of the study. A thin cellophane bag filled with warm water was used as an acoustic interface between the transducer and the heart (8). The position of the transducer on the epicardial surface was marked with the aid of silk sutures to identify the proper cross-sectional plane for subsequent assessment of the hypoperfused region and for regional myocardial blood flow measurements. The imaging plane depth and gain settings were optimized at the beginning of the study and were not changed during the remainder of the protocol. All images before and during injections of contrast material were recorded on 0.5-in.- (1.27 cm-) VHS tape for later analysis.

Table 1. Presence and Absence of Perfusion Defects During Occlusion and Stenosis and Their Relation to Percent Reduction in Coronary Reserve Ratio in 16 Dogs

Dog No.	Anatomic* Area at Risk	Myocardial Contrast Echocardiography*			% Reduction in CRR
		Occlusion	Dipyridamole + Stenosis	SPECT* Stenosis	
1	42.7	ND	52.8	41	98
2	21.8	18.8	16.7	NA	55
3	26.7	22.7	21.4	NA	0
4	35.2	47.6	39.7	30.0	4
5	52.3	38.4	41.8	30.0	47
6	63	65.3	58.6	50.0	82
7	33	37	0	19.3	7
8	19.6	0	0	9.5	50
9	39.2	37	0	44	34
10	55.9	47.9	35.2	42	78
11	48.2	35.1	31.6	36.5	50
12	58.8	46.1	35.2	46.5	77
13	36	26.3	0	25.6	0
14	20.1	19.1	15.9	24.5	28
15	41	31	28.5	22	69
16	58	24	21	14	79
Total Mean	40.7	35	25	31	47
SD	14.3	15.6	18.9	12	32

*All values for the three techniques are expressed as percent of total left ventricular area at mid-papillary muscle level. CRR = coronary reserve ratio; NA = not able to analyze; ND = not done; SPECT = single-photon emission computed tomography.

The contrast agent used consisted of a commercial preparation of a sonicated 5% human serum albumin solution (Albunex) provided by Molecular Biosystems. The air-filled microspheres produced by this process have been shown to remain stable up to 20 weeks at room temperature. These microbubbles do not alter the baseline coronary blood flow in dogs when they are injected into the coronary arteries in volumes up to 2.4 ml (9). They have an average diameter of 4 ± 1 μm and are contained in a sterile aqueous solution in a concentration of 400×10^6 spheres/ml (Molecular Biosystems, unpublished data).

An ECG-gated flow injector (Medrad) was used to perform R wave-triggered power injection of the contrast agent. The injector was connected through plastic tubing prefilled with 0.9% sodium chloride to the modified pigtail catheter located in the aortic root. For each dog, a volume of sonicated albumin (range 0.25 to 2 ml) was selected whose injection into the aortic root produced good opacification of the left ventricular myocardium at baseline; this volume was held constant during all injections throughout the study. To avoid respiratory motion of the heart, the respirator was turned off at the end of the inspiratory cycle during the contrast injections. Measurements of arterial blood pressure, heart rate and Doppler flow velocities were obtained simultaneously with myocardial contrast echocardiography at the following times: 1) during the baseline state (n = 16), 2) during a 20-s occlusion of either the left anterior descend-

ing (n = 7) or circumflex (n = 8) artery, 3) after establishment of a coronary stenosis (n = 16), and 4) at the peak of the dipyridamole-induced hyperemia as assessed by Doppler flow velocity in the control region (n = 16). Dipyridamole was given as a 0.84 mg/kg intravenous bolus injection.

Radioactive microspheres (15 μm in diameter) were injected into the left atrium at baseline, after creation of the stenosis and at the peak of the dipyridamole-induced hyperemia. The microspheres used (3M Co.) were labeled with ruthenium-105, niobium-95 and cerium-141. A reference blood sample was withdrawn with a Harvard pump from the carotid line, beginning 30 s before each microsphere injection and continuing for 3 min at a rate of 4.05 ml/min (8).

SPECT thallium imaging. The excised heart was placed directly under the SPECT gamma camera. Images were acquired over a 180° arc, beginning in the 45° left posterior oblique position and ending in the 45° right anterior oblique position. A total of 30 images 6° apart were acquired at a rate of 20 s/image. The data were stored on a 64 × 64 × 8 byte matrix. Transaxial reconstruction was performed by a back-projection technique with a Butterworth (order 5) high pass filter/low pass window and a 50% cutoff. The reconstructed tomographic slices (6 mm thick) were reoriented in the short axis and the individual slices displayed sequentially on a large color oscilloscope.

Tissue processing. The site of the stenosis was identified on the epicardial vessel with the aid of a silk tie. A polyethylene catheter was advanced into the arterial segment distal to the coronary stenosis site and 200 ml of Macrodex (6% dextran 70 in normal saline solution) was infused through it to delineate the ischemic area (unstained); 200 ml of monastral blue dye was infused into the arterial segment proximal to the stenosis to delineate the normally perfused or control area (stained blue). The two vascular beds were perfused simultaneously for 1.5 min at a pressure of 260 mm Hg to prevent flow through collateral vessels until an even discoloration of the myocardium was noted. The distance from the apex to the silk sutures was recorded for each dog. After completion of the thallium imaging, the heart was cut along its short axis into 10-mm thick slices, and the slice corresponding to the echocardiographic imaging plane (identified by the silk sutures placed in the epicardium) was used as the selected anatomic slice.

The selected anatomic slice was placed over an acetate sheet on which 24 equal segments were drawn. These were labeled in a counterclockwise manner, starting at the anterior papillary muscle. Two regions containing 5.8 ± 1 segments each, one in the center of the "ischemic" region and one in the center of the control region, were selected. The tissue slice was photographed with the distal surface facing the camera. After this procedure, the papillary muscles were excised and the anatomic slice was cut into 24 equal samples. The resulting tissue samples containing the preselected control and "ischemic" regions were placed into 5-ml test tubes of known weight containing 3.5 ml of formalin as a preservative. The tissue and the reference arterial blood samples were counted on a gamma well counter.

Myocardial blood flow (MBF), in ml/min per g, was calculated for each nuclide using the formula: MBF = Cm × RBF/Cr, where Cm = counts/min per gram in myocardial tissue samples, RBF = reference blood flow in ml/min (Harvard pump withdrawal rate) and Cr = counts/min in the reference blood sample (10). The amount of dipyridamole-induced hyperemia in the control and ischemic regions was determined as the postdipyridamole myocardial blood flow divided by the baseline flow and expressed as a coronary reserve ratio. The percent reduction in coronary reserve ratio (CRR) was used as an index of severity of coronary stenosis and was derived as:

$$\frac{\text{CRR (control region)} - \text{CRR (ischemic region)}}{\text{CRR (control region)}} \times 100.$$

A color slide of the anatomic 10-mm thick slice was projected into a screen and the endocardial and epicardial contours were manually drawn over a plastic overlay. The overlay was placed on a tablet digitizer and the ischemic area (hypoperfused area) was determined by planimetry. Risk area was expressed as a percent of the left ventricular area. All measurements were made by an investigator unaware of the echocardiographic or thallium-201 SPECT results.

Quantitative analysis of echocardiographic images (Fig. 1). The recorded echocardiographic images were played back on an off-line computer station equipped with internal calipers (Microsonics, model CAD 886 AT). Starting with three cardiac cycles before the appearance of contrast in the myocardium, 32 sequential end-diastolic frames were digitized and placed in a cine loop format. This format facilitated the differentiation of normally perfused (positive contrast effect) from hypoperfused (absent or diminished contrast effect) myocardium (Fig. 1). The end-diastolic frame showing the largest perfusion defect was selected for analysis. The area of underperfusion (risk area) was determined by planimetry and expressed as a percent of the left ventricular area at the papillary muscle level. To assess the inter- and intraobserver variability of the risk area by myocardial contrast echocardiography, measurements were repeated by a second independent investigator (15 injections) and by the initial investigator 2 months later (16 injections). The measurement error is reported as the coefficient of variation.

Wall motion assessment (Table 2). To determine the hemodynamic significance of the perfusion defects seen by contrast echocardiography and by thallium-201 SPECT, the images were analyzed for the presence or absence of wall motion abnormalities during baseline, after coronary occlusion and during coronary stenosis (before and after the administration of dipyridamole). The analysis of regional wall motion was performed with an off-line computer station (Digisonics). An epicardial centroid was used to determine the percent shortening fractions along the segments studied by contrast echocardiography (8).

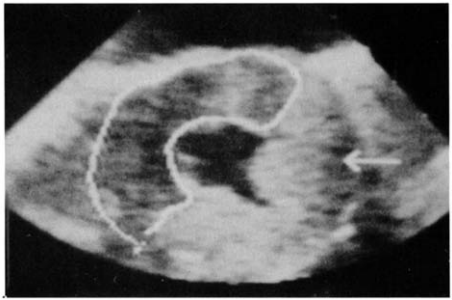

Figure 1. Diastolic frame of the echocardiographic short-axis view of the left ventricle at mid-papillary muscle level. The planimetry-determined area constitutes the area of relative underperfusion observed after the administration of dipyridamole and in the presence of stenosis of the left anterior descending coronary artery. The **arrow** points to an area of lateral dropout.

Quantitative analysis of SPECT thallium images. For each dog, short-axis slices were selected for analysis by matching the distance from the apex to the site of the coronary stenosis, identified by epicardial silk sutures on the excised heart. To enhance the visual perception of the myocardium, the images were temporarily smoothed with a 3 × 3 filter. Contrast and background levels were manually adjusted to afford optimal myocardial edge recognition. Using a light pen, a single investigator unaware of the anatomic and echocardiographic results manually traced two regions of interest, one covering the left ventricular myocardium excluding the left ventricular cavity, and the other including only the underperfused area. The computer automatically determined the number of pixels and expressed the size of the perfusion defect as a percent of the total number of pixels in the left ventricular slice of interest. Excellent low values for intra- and interobserver variability have been previously reported (11) for this quantitative analysis from our laboratory.

Statistical analysis. Correlations between measurements of perfusion defects by myocardial contrast echocardiography and thallium-SPECT versus anatomic area at risk were made by linear regression analysis. Analysis of variance was used to analyze significant changes in regional wall motion. Significance was established at $p < 0.05$.

Table 2. Regional Wall Motion (% shortening fraction) in the Control and Ischemic Zones During Various Interventions and Its Relation to Coronary Reserve Ratio in 16 Dogs

Dog No.	Baseline		Occlusion		Stenosis		Dipyridamole + Stenosis	
	CZ	IZ	CZ	IZ	CZ	IZ	CZ	IZ
1	13	17	--	—	10	14	21	4
2	20	22	26	18	38	25	29	30
3	26	27	16	0	29	34	32	14
4	14	14	13	−16	24	25	24	23
5	26	33	14	20	28	39	38	50
6	26	13	21	−5	59	11	18	10
7	15	12	23	1	20	20	28	9
8	25	24	19	15	31	36	29	33
9	33	14	42	0	49	11	49	40
10	19	13	11	−11	26	19	21	15
11	23	15	17	−2	25	27	24	5
12	21	12	15	−5	32	12	20	16
13	30	28	28	−1	31	35	51	39
14	21	14	42	−4	43	49	30	34
15	14	19	20	0	25	20	33	20
16	35	44	28	−36	36	46	57	56
Mean	22	20	22	−2	31	26	31	25
SD	6.7	9.1	9.5	13.7*	11.6	12.2	11.7	16

CZ = control zone; IZ = ischemic zone. *$p < 0.05$ versus value in the control zone.

Results

Hemodynamic changes during interventions. The heart rate at baseline was 137 ± 18 beats/min and did not change after coronary occlusion (141 ± 16 beats/min, p = NS). Similarly, mean arterial blood pressure did not vary significantly from baseline conditions to coronary occlusion (112 ± 22 vs. 103 ± 24 mm Hg, respectively, p = NS). In the presence of stenoses of variable severity, the administration of dipyridamole significantly decreased both heart rate (130 ± 15 beats/min, p = 0.009) and mean arterial blood pressure (87 ± 16 mm Hg, p = 0.001) in comparison with baseline values. Similar hemodynamic changes after dipyridamole administration have been previously reported (8).

Risk area measurements (Table 1). During transient complete occlusion, an area of underperfusion (Fig. 2) was observed by myocardial contrast echocardiography in 14 of 15 dogs (1 dog did not have a contrast injection during occlusion). The size of the perfusion defect correlated significantly ($r = 0.74$; $p < 0.002$) with the anatomic area at risk. An area of relative underperfusion was detected by myocardial contrast echocardiography in 12 of the 16 dogs with a variable stenosis after administration of dipyridamole (Fig. 3). The degree of coronary flow disturbance was defined by

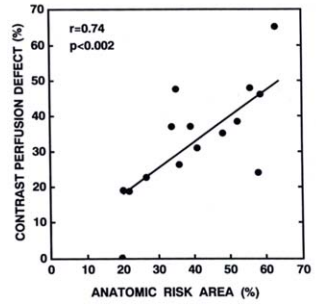

Figure 2. Correlation between the anatomic area at risk (x axis) and the echocardiographic perfusion defect (y axis) in the presence of a coronary occlusion in 15 of the 16 dogs.

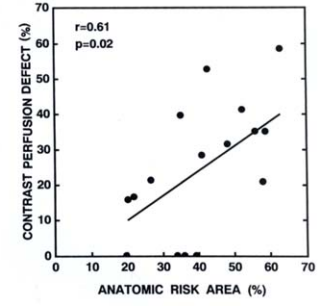

Figure 3. Correlation between the anatomic area at risk (x axis) and the echocardiographic perfusion defect (y axis) in the presence of a coronary stenosis and after administration of dipyridamole in 16 dogs.

the percent reduction in coronary reserve ratio and was severe (75% to 100% reduction) in five dogs, moderate (50% to 74% reduction) in four and mild (0% to 49% reduction) in seven. Of the 12 dogs with a contrast perfusion defect after injection of dipyridamole during coronary stenosis, 5 had a severe reduction in hyperemic flow, 3 had a moderate reduction and 4 had a mild reduction. All four dogs without a perfusion defect by myocardial contrast echocardiography had a reduction in coronary reserve of ≤50%; one of them was the same dog without a perfusion defect during complete coronary occlusion. The coronary flow reserve ratio in the control and ischemic regions in the 12 dogs with a perfusion defect by myocardial contrast echocardiography was 3.54 ± 1.81 and 1.31 ± 0.83, respectively ($p = 0.001$), and in the 4 dogs without a perfusion defect, 4.71 ± 3.71 and 3.71 ± 3.68, respectively (p = NS). The correlation between the anatomic risk area and the underperfused area measured by myocardial contrast echocardiography for all 16 dogs was significant ($p = 0.02$) with a correlation coefficient of 0.61 (Fig. 3). Values for intra- and interobserver variability for area at risk measured by myocardial contrast echocardiography in the presence of both occlusion and variable stenosis were 4.1% and 6.6%, respectively.

The area at risk measured by SPECT-thallium imaging during dipyridamole stenosis correlated significantly (Fig. 4) with the anatomic area at risk ($r = 0.58$; $p = <0.03$). In two dogs, the thallium images could not be analyzed because of low thallium counts, possibly due to faulty injections. In all other dogs, a perfusion defect was detected by thallium-201, ranging in size from 9.5% to 50% of the left ventricle at the papillary muscle level. The correlation between contrast echocardiography and tomographic thallium imaging for the measurement of area at risk in the presence of a variable stenosis during dipyridamole-induced hyperemia ($r = 0.58$; $p = 0.025$) was similar to the correlation observed between myocardial contrast echocardiography and anatomic risk area. An example of the perfusion defect by SPECT and the corresponding anatomic area at risk is shown in Figure 5.

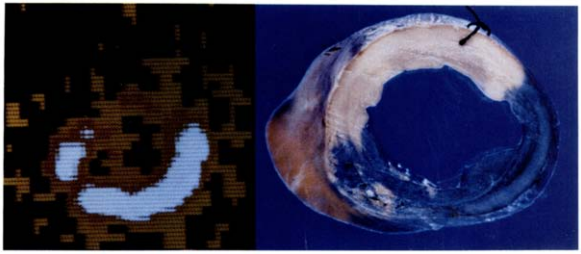

Figure 4. Thallium imaging (**left**) and anatomic slice counterpart (**right**) of Figure 1. **Left,** Area at risk by thallium imaging appears as **black** (absence of counts) and the control area as **white. Right,** Anatomic area at risk is **unstained,** whereas the control area is delineated by the **blue** stain.

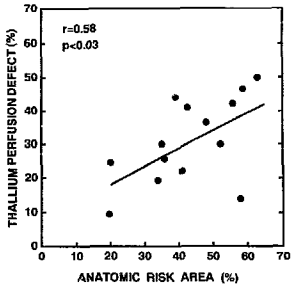

Figure 5. Correlation between the anatomic area at risk (x axis) and the SPECT thallium perfusion defect (y axis) in the presence of a coronary stenosis and after administration of dipyridamole in 14 dogs.

Wall motion abnormalities (Table 2). No dog exhibited wall motion abnormalities at baseline, and shortening fraction was not significantly different in the control (22 ± 6.7%) and ischemic (20 ± 9.1%) zones. No significant changes in shortening fraction were observed with any of the interventions in the control zone. During transient complete occlusion, 14 of the 15 dogs developed a new wall motion abnormality in the ischemic zone that was associated with a significant decrease in overall shortening fraction. Although a marked reduction in shortening fraction was observed in the ischemic zone of some animals during coronary stenosis with or without dipyridamole administration, the change was not significant for the entire group.

Discussion

Estimating the area of underperfusion after coronary stenosis. The present study demonstrates that sonicated human albumin (Albunex) can be used as a myocardial contrast agent to detect and estimate the size of areas of underperfused myocardium in the presence of a complete coronary occlusion with an accuracy similar to that shown by other investigators (2–7) using other contrast agents. All but 1 of the 15 dogs subjected to temporary coronary occlusion had a visible perfusion defect whose size correlated with the anatomic area at risk by the dual perfusion technique. The dog without a perfusion defect by myocardial contrast echocardiography had a small anatomic area at risk (<20% of the left ventricular anatomic slice) that could have been even smaller in vivo as a result of the effect of collateral flow (12).

Previous investigations by our group (8) and others (13) using sonicated meglumine diatrizoate have shown that myocardial contrast echocardiography can detect relative myocardial underperfusion in myocardial regions supplied by an artery with a critical stenosis after the administration of a potent coronary arteriolar dilator. The current study demonstrates for the first time the capacity of myocardial contrast echocardiography performed with sonicated albumin microspheres to identify regions of underperfusion in the territory supplied by a coronary artery with less than a critical flow limitation. The limitation in hyperemia induced by the stenosis ranged from mild to severe, but was noncritical in 11 of the 16 dogs. Myocardial areas with reduced contrast intensity were visualized in 12 of the 16 dogs. The four dogs without visible hypoperfusion had a coronary reserve reduction of ≤50%. Furthermore, a significant relation was found between the size of the perfusion defect and the anatomic area at risk. The contrast echocardiographic perfusion defect, however, underestimated the anatomic area at risk in 10 of the 12 dogs that demonstrated such a defect.

SPECT thallium imaging versus contrast echocardiography. A perfusion defect was observed with SPECT-thallium imaging in all 14 dogs analyzed, suggesting that this technique was more sensitive than myocardial contrast echocardiography in detecting perfusion defects produced by coronary stenoses. The size of the perfusion defect by SPECT-thallium correlated significantly with the anatomic risk area with a regression coefficient similar to that found with myocardial contrast echocardiography, but lower than that previously reported by Prigent et al. (14) with thallium-201 and Verani et al. (11) using technetium-99m hexakis 2-methoxyisobutyl isonitrile (hexa MIBI). This result was expected because those studies compared the scintigraphic perfusion defect during coronary occlusion with pathologic infarct size, whereas our experimental protocol required that we compare the scintigraphic perfusion defect during variable degrees of severity of coronary stenosis with the size of the occluded anatomic vascular bed, which is independent of collateral blood flow. An example of this limitation was observed in one dog (Dog 16), which demonstrated a small echocardiographic perfusion defect during coronary occlusion and after injection of dipyridamole during coronary stenosis as well as a small perfusion defect by thallium imaging. Conversely, the anatomic area at risk in this dog was >50% of the left ventricular slice studied. If this dog is excluded from the analysis, the correlation between the anatomic area at risk and thallium imaging ($r = 0.80$) and between risk area and contrast echocardiography (occlusion, $r = 0.85$; dipyridamole stenosis, $r = 0.67$) improved considerably. As with myocardial contrast echocardiography, SPECT underestimated the anatomic area at risk in 13 of the 14 dogs analyzed. These findings further warrant the concept that both of these imaging techniques demonstrate a "functional" rather than an anatomic area at risk produced by less than critical coronary stenoses.

Implications. The low frequency of wall motion abnormalities observed after dipyridamole injection during stenosis suggests that contrast echocardiography in the presence of a potent coronary arteriolar vasodilator detects a perfusion abnormality before ischemia develops and may there-

fore be a more sensitive test than the assessment of regional wall motion. These findings support further studies to determine whether myocardial contrast echocardiography with sonicated albumin can be used clinically to distinguish coronary stenosis of varying degrees of severity after the administration of a potent coronary arteriolar vasodilator. Administration of the contrast agent directly into the coronary arteries instead of the aortic root may facilitate standardization of the volume (and thus the number of microbubbles) required for injection in different patients and thus improve the reproducibility of results. This could lead to the application of myocardial contrast echocardiography in the evaluation of the physiologic importance of an angiographic lesion.

Limitation. In this study, only one degree of stenosis was created in each dog. This protocol was followed because this investigation was designed to compare the results of contrast echocardiography with the results of SPECT thallium-201 imaging and thallium, as a result of its long half-life, cannot be injected more than once in any dog.

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